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TRANSMITTAL FORM

Application Serial Number	10/072,634
Filing Date	February 8, 2002
First Named Inventor	Steitz
Group Art Unit	1631
Examiner Name	Channing Mahatan
Attorney Docket No.	RIB-005
Patent No.	6,952,650
Issue Date	October 4, 2005

ENCLOSURES ***(check all that apply)***

- ☐ Fee Transmittal Form
  - ☐ Check Attached
  - ☐ Copy of Fee Transmittal Form
- ☐ Amendment/Response
  - ☐ Preliminary
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
  - ☐ Letter to Official Draftsperson including Drawings [Total Sheets _____]
- ☐ Petition for Extension of Time
- ☐ Information Disclosure Statement
  - ☐ Form PTO-1449
  - ☐ Copies of IDS Citations
- ☐ Certified Copy of Priority Document(s)
- ☐ Sequence Listing submission
  - ☐ Paper Copy/CD
  - ☐ Computer Readable Copy
  - ☐ Statement verifying identity of above
- ☐ Copy of Notice to File Missing Parts of Application
- ☐ Formal Drawing(s)
- ☐ Request For Continued Examination (RCE) Transmittal
- ☐ Power of Attorney (Revocation of Prior Powers)
- ☐ Terminal Disclaimer
- ☐ Executed Declaration and Power of Attorney for Utility or Design Patent Application
- ☐ Small Entity Statement
- ☐ CD(s) for large table or computer program
- ☐ Amendment After Allowance
- ☒ Request for Certificate of Correction
  - ☒ Certificate of Correction
- ☐ Notice of Appeal to Board of Patent Appeals and Interferences
- ☐ Appeal Brief (in triplicate)
- ☐ Status Inquiry
- ☒ Return Receipt Postcard
- ☒ Certificate of First Class Mailing under 37 C.F.R. 1.8
- ☐ Certificate of Facsimile Transmission under 37 C.F.R. 1.8
- ☒ Additional Enclosure(s) *(please identify below)*
  - Copy of Amendment and Response filed May 19, 2004

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Respectfully submitted,

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PATENT
Attorney Docket No. RIB-005

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS:	Steitz *et al.*	CONFIRMATION NO.:	5341
PATENT NO.:	6,952,650	GROUP NO.:	1631
ISSUE DATE:	October 4, 2005	EXAMINER:	Channing Mahatan
TITLE:	Modulators of Ribosomal Function and Identification Thereof		

CERTIFICATE OF FIRST CLASS MAILING UNDER 37 C.F.R. 1.8

I hereby certify that this correspondence, and any document(s) referred to as enclosed herein, is/are being deposited with the United States Postal Service as first class mail, postage prepaid, in an envelope addressed to Certificate of Correction Branch, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 30th day of November, 2005.

Carrah Malone

Carrah Malone

ATTN: Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Submitted herewith is/are:

1. Transmittal Form (1 pg.);
2. Request for Certificate of Correction Under 35 U.S.C. § 254 and 37 C.F.R. § 1.322 (2 pgs.);
3. Certificate of Correction (1 pg.);
4. Copy of Amendment and Response filed May 19, 2004 (18 pgs.); and
5. Return receipt postcard.

LIBC/2627256.1

PATENT
Attorney Docket No.: RIB-005

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

INVENTOR:	Steitz *et al.*		
PATENT NUMBER:	6,952,650	CONFIRMATION NO.:	5341
ISSUE DATE:	October 4, 2005	GROUP NO.:	1631
SERIAL NO.:	10/072,634	EXAMINER:	Channing Mahatan
FILING DATE:	February 8, 2002		
TITLE:	Modulators of Ribosomal Function and Identification Thereof		

ATTN: Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION UNDER
35 U.S.C. § 254 and 37 C.F.R. § 1.322

Applicants hereby request the Office to issue a certificate of correction pursuant to 35 U.S.C. § 254 and 37 C.F.R. § 1.322 to correct mistakes appearing on the face and in claim 24 of the above-identified patent. Specifically, the face of the patent in section "(75) Inventors" mistakenly includes Joseph A. Ippolito as an inventor, and claim 24 contains a typographical error in the word, "molpcule."

With regard to the inventorship, Applicants, on page 14 of an Amendment and Response dated May 19, 2004 (copy enclosed), requested amending the inventorship of the application pursuant to 37 C.F.R. § 1.48(b) to delete Joseph A. Ippolito from the inventive entity because his invention was no longer being claimed in the application.

In addition, claim 24 includes a printing error where the word "molecule" is misspelled "molpcule." Claim 24 was introduced into the case as claim 107 via the May 19, 2004 Amendment and Response. On page 12 of the Amendment and Response, Applicants introduced new claim 107, which correctly spells the word "molecule" in the preamble.

Applicants submit that the foregoing corrections appear in the enclosed Certificate of Correction (PTO/SB/44) form and respectfully request that the Office issue a Certificate of Correction reflecting the corrections as they appear on the attached form. Applicants believe that these printing errors were caused by the Office, and that no fee is due for the Certificate of Correction. However, if a fee is required, the Office is authorized to charge the fee to Deposit Account No. 07-1700.

The Office is invited to contact the undersigned with any questions about this submission.

Respectfully submitted,

Date: November 30, 2005

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.: 6,952,650 B2
ISSUE DATE: October 4, 2005
INVENTORS: Thomas A. Steitz, Peter B. Moore, Nenad Ban, Poul Nissen, Jeffrey Hansen, and Joseph A. Ippolito (this last inventor currently listed in error by the U.S. Patent and Trademark Office)

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the face of the patent, in section (75), delete "; **Joseph A. Ippolito**, Guilford, CT (US)"

In claim 24, column 137, line 11, delete "molpcule" and insert --molecule--.

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PATENT NO.: 6,952,650 B2

Express Mail Mailing Label No. EV219996058US

PATENT
Attorney Docket No. RIB-005
(7995/7)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS:	Steitz *et al.*		
SERIAL NO.:	10/072,634	GROUP NO.:	1631
FILING DATE:	February 8, 2002	EXAMINER:	Channing Mahatan
TITLE:	Ribosome Structure and Protein Synthesis Inhibitors		

Mail Stop Amendment
Commissioner for Patents
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AMENDMENT AND RESPONSE

This paper is responsive to the Office Action for the above-identified patent application, mailed from the Office on February 25, 2004. Applicants believe that no extension of time is necessitated by this submission.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims begin on page 8 of this paper.

Remarks begin on page 13 of this paper.

Amendments to the Specification:

On page 1 of the specification, delete the title starting with "RIBOSOME STRUCTURE" and ending with "INHIBITORS" and replace with the following new title:

-- MODULATORS OF RIBOSOMAL FUNCTION AND IDENTIFICATION THEREOF --

On page 1, immediately after the heading **REFERENCE TO RELATED APPLICATIONS**, replace the paragraph beginning with "This application" and ending with "reference herein." with the following new paragraph:

-- This application is a continuation-in-part of co-pending application of U.S. Application No. 09/922,251, filed August 3, 2001, and claims the benefit of (i) U.S. Provisional Application No. ~~[Attorney Docket No. RIB-003PR]~~ 60/348,731, filed January 14, 2002, and (ii) U.S. Provisional Application No. ~~[Attorney Docket No. RIB-004PR]~~ 60/352,024, filed January 25, 2002, the disclosures of each of which are incorporated by reference herein. --

Please amend the paragraph bridging pages 13 and 14 to read as follows:

-- In a preferred embodiment, the atomic co-ordinates further define at least a portion of a protein synthesis inhibitor, for example, an antibiotic, more specifically an antibiotic selected from the group consisting of anisomycin, blasticidin, carbomycin A, sparsomycin, spiramycin, tylosin, virginiamycin M, azithromycin, linezolid, chloramphenicol and erythromycin, complexed with a ribofunctional locus. More specifically, the invention provides atomic co-ordinates of the large ribosomal subunit together the atomic co-ordinates of antibiotics interacting with the large ribosomal subunit. These atomic co-ordinates are recorded on compact disk, Disk No. 1, and correspond to: large ribosomal subunit complexed with anisomycin (file name: anisomysin.pdb or ANISOMYC.PDB); large ribosomal subunit complexed with blasticidin (file name: blasticidin.pdb [[~~,~~]] or BLASTICI.PDB); large ribosomal subunit complexed with carbomycin (file name: carbomycin.pdb or CARBOMYC.PDB); large ribosomal subunit complexed with tylosin (file name: tylosin.pdb or TYLOSIN.PDB); large ribosomal

subunit complexed with sparsomycin (file name: sparsomycin.pdb or SPARSOMY.PDB); large ribosomal subunit complexed with virginiamycin M (file name: virginiamycin.pdb or VIRGINIA.PDB); large ribosomal subunit complexed with spiramycin (file name: spiramycin.pdb or SPIRAMYC.PDB); large ribosomal subunit complexed with azithromycin (file name: AZITHROM.PDB or azithromycin.pdb); or large ribosomal subunit complexed with linezolid (file name: LINEZOLI.PDB or linezolid.pdb); or large ribosomal subunit complexed with erythromycin (file name: erythromycin.pdb). --

Please amend the paragraph bridging pages 32 and 33 to read as follows:

-- As used herein, the term "atomic co-ordinates" or "structure co-ordinates" refers to mathematical co-ordinates (represented as "X," "Y" and "Z" values) that describe the positions of atoms in a crystal of a ribosome or ribosomal subunit. The diffraction data obtained from the crystals are used to calculate an electron density map of the repeating unit of the crystal. The electron density maps are used to establish the positions of the individual atoms within a single ribosomal subunit. Those of skill in the art understand that a set of structure co-ordinates determined by X-ray crystallography is not without standard error. For the purpose of this invention, the structures of two ribosomes, ribosomal subunits or portions thereof are considered to be the same if they satisfy one of the following two tests. In a first test, the structures are considered to be the same if a set of structure co-ordinates for a ribosome or ribosomal subunit from any source has a root mean square deviation of non-hydrogen atoms of less than about 2.0 Å, or more preferably less than about 0.75 Å, when superimposed on the non-hydrogen atom positions of the atomic co-ordinates deposited at the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (PDB) (Berman *et al.* (2000) *Nucleic Acids Research* 28, 235-242; see also, the web page at URL ~~http://www.~~rcsb.org/pdb/) with the accession numbers PDB ID: 1FFK; PDB ID: 1FFZ; PDB ID: 1FG0; PDB ID: 1JJ2;PDB ID: 1K73; PDB ID: 1KC8; PDB ID: 1K8A; PDB ID: 1KD1; or PDB ID: 1K9M, or contained on Disk 1 of 1, the disclosure of each of the foregoing of which is incorporated herein by reference in its entirety. In a second test, the structures are considered to be the same if the r.m.s. deviation between a set of atoms in a test structure and a corresponding set of atoms in a reference structure is less than 2.0 Å. For the purposes of this test, the set of atoms in the reference structure comprises at least

five of the series of 23S rRNA residues listed below as 631-633, 835-841, 844-846, 882-885, 1836-1839, 2095-2105, 2474-2478, 2485-2490, 2528-2530, 2532-2543, 2607-2612, 2614-2623, 2642-2648 of the structure deposited in the PDB under accession number PDB ID: 1JJ2 or contained as file name ~~1jj2.rtf~~ 1JJ2.RTF on Disk 1 of 1. The residues in the test structure corresponding to the ones listed above are identified by sequence alignment using the program Lasergene v. 5.0 (DNA Star, Inc., Madison, WI) with the default settings. Specifically, the computer program is used to align those residues listed above in the *Haloarcula marismortui* 23S rRNA sequence with those in the test organism's rRNA. Once aligned, the corresponding residues in the test organism's rRNA are identified. The atomic co-ordinates of backbone atoms (P, C5', 05', C4', C3', 03') of atoms in the test structure are superimposed upon the corresponding backbone atoms (P, C5', 05', C4', C3', 03') of the reference structure using the program MIDAS Plus (Ferrin *et al.* (1988) *J. Mol. Graphics* 6: 13-27 and 36-37). The test and reference structures are considered the same if the r.m.s. deviation between the two sets of atoms after superpositioning is less than 2.0 Å, as determined by MIDAS Plus. --

Please amend the first full paragraph appearing on page 34 to read as follows:

-- Reference is made to the sets of atomic co-ordinates and related tables included with this specification and submitted on compact disk (two total compact disks including one original compact disk, and a duplicative copy of original compact disks). Disk No. 1 contains thirty-nine files. Disk No 1 contains the files identified as PDB1FFK.DOC and PDB1FFK.ENT which represent files of co-ordinates defining the large ribosomal subunit; PDB1FFZ.DOC and PDB1FFZ.ENT which represent files of the co-ordinates defining the large ribosomal subunit - CCdA-p-Puro complex; and PDB1FGO.DOC and PDB1FGO.ENT which represent files of the co-ordinates defining the large ribosomal subunit - aa-tRNA analogue complex; 1JJ2.RTF and 1JJ2.TXT which represent files of the co-ordinates defining the completely refined large ribosomal subunit; anisomycin.pdb, blasticidin.pdb, carbomycin.pdb, sparsomycin.pdb, spiramycin.pdb, tylosin.pdb and virginiamycin.pdb which represent files of the co-ordinates defining the large ribosomal subunit bound to anisomycin, blasticidin, carbomycin, sparsomycin, spiramycin, tylosin, and virginiamycin, respectively; three folders: FOLDERA contains the file identified as 1JJ2.PDB (which represents a file of a more highly refined co-ordinates defining the

large ribosomal subunit), FOLDERB contains the files identified as ANISOMYC.PDB, BLASTICI.PDB, CARBOMYC.PDB, SPARSOMY.PDB, SPIRAMYC.PDB, TYLOSIN.PDB, and VIRGINIA.PDB (which represent files of the refined co-ordinates defining the large ribosomal subunit bound to anisomycin, blasticidin, carbomycin, sparsomycin, spiramycin, tylosin, and virginiamycin, respectively), FOLDERC contains the files identified as AZITHROM.PDB, and LINEZOLI.PDB (which represent files of the co-ordinates defining the large ribosomal subunit bound to azithromycin and linezolid, respectively); the file identified as erythromycin.pdb (which represents a file of the co-ordinates defining the large ribosomal subunit bound to erythromycin), and azithromycin.pdb and ~~linezolid.pdp~~ linezolid.pdb (which represent files of the refined co-ordinates defining the large ribosomal subunit bound to azithromycin and linezolid, respectively). --

Please amend the first full paragraph appearing on page 37 to read as follows:

-- As used herein, the term "homologue" is understood to mean any one or combination of (i) any protein isolated or isolatable from a ribosome or a ribosomal subunit (*i.e.*, a ribosomal protein), (ii) any nucleic acid sequence isolated or isolatable from a ribosome or ribosomal subunit (*i.e.*, a ribosomal RNA), (iii) any protein having at least 25 % sequence identity to a ribosomal protein isolated from *E. coli* or *Rattus norvegicus* as determined using the computer program "BLAST" version number 2.1.1 implementing all default parameters, or (iv) any nucleic acid having at least 30% sequence identity to a ribosomal RNA isolated from *E. coli* or *Rattus norvegicus* as determined using the computer program "BLAST" version number 2.1.1 implementing all default parameters. "BLAST" version number 2.1.1 is available and accessible via the world wide web at ~~http://www/~~ the URL ncbi.nlm.nih.gov/BLAST/ or can be run locally as a fully executable program on a standalone computer. --

Please amend the paragraph bridging pages 40 and 41 to read as follows:

-- The present invention is also based, in part, on the atomic structure of the crystal of the 50S ribosomal subunit from *H. marismortui* that has been derived from a 2.4 Å resolution electron density map that was experimentally phased using heavy atom derivatives. The atomic co-ordinates defining the large ribosomal unit were deposited on July 10, 2000, at Research

Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (PDB) (Berman *et al.* (2000) *Nucleic Acid Research* 28, 235-242; ~~http:// www.~~ see also, the web page at the URL rcsb.org/pdb/) with accession number PDB ID: 1FFK. --

Please amend the second full paragraph appearing on page 57 to read as follows:

-- Analysis of the atomic co-ordinates discussed in section IIA above together with additional atomic co-ordinates of a ribosomal subunit complexed with various analogues, similarly refined, permit an analysis of ribosome function. Accordingly, the present invention is also based on the crystals of *Haloarcula marismortui* 50S ribosomal subunit complexed either with the Yarus transition state analogue, CCdA-p-Puro, or with a mini-helix analogue of an aminoacyl-tRNA. The present invention provides the structures of both complexes. The atomic co-ordinates of the structure of both complexes were deposited on July 26, 2000, at Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (PDB) (Berman *et al.* (2000) *Nucleic Acid Research* 28: 235-242; ~~http:// www.~~ see also, the web page at the URL rcsb.org/pdb/) with accession numbers PDB ID: 1FFZ (50S ribosome/ CCdA-p-Puro complex) and PDB ID: 1FG0 (50S ribosome/aa-tRNA analogue). --

Please amend the paragraph bridging pages 81 and 82 to read as follows:

-- By way of example, since the nucleotide sequences of all known 50S subunit rRNAs can be aligned relative to each other and to *H. marismortui* 23S and 5S rRNAs, it is possible to construct models of the structures of other 50S ribosomal rRNAs, particularly in the regions of the tunnel and active sites, using the *H. marismortui* structure. Likewise, homologous proteins can also be modeled using similar methodologies. Methods useful for comparative RNA sequence analysis are known in the art and include visual methods and number pattern methods, as well as methods employing chi-square statistics, phylogenetic algorithms, or empirical algorithms. Descriptions of some of the foregoing methods are available, for example, ~~at http://www.~~ on the world wide web at the URL rna.icmb.utexas.edu/; Gutell (1996), "Comparative Sequence Analysis and the Structure of 16S and 23S rRNA," Ribosomal RNA. Structure, Evolution, Processing, and Function in Protein Biosynthesis, (Dahlberg A. and Zimmerman B., eds.) CRC Press. Boca Raton, pp. 111-128; Guttell *et al.* (1993) *Nucl. Acid Res.*

21:3055 - 3074; Schnare *et al.* (1996) *J. Mol. Biol.* 256: 701-719. Particularly useful visual inspection methods include comparison of a particular position in a *H. marismortui* secondary structure diagram with the residues located at the analogous position on an *E. coli* secondary structure diagram. A software program that is particularly useful in homology modeling includes XALIGN (Wishart, D. *et al.*, (1994) *Cabios* 10: 687-88). See also, U.S. Patent No. 5,884,230. --

Please amend the second full paragraph appearing on page 184 to read as follows:

-- The disclosure of each of the patent documents, scientific articles, atomic-co-ordinates (including, without limitation, those sets deposited at the Research Collaboratory for Structural Bioinformatics Protein Data Bank (PDB) with the accession numbers PDB ID: 1FFK; PDB ID: ~~1FF2~~ 1FFZ; PDB ID: 1FG0; PDB ID: 1JJ2; PDB ID: 1K73; PDB ID: 1KC8; PDB ID: 1K8A; PDB ID: 1KD1; and PDB ID: 1K9M, and/or contained on Disk No. 1) referred to herein is incorporated by reference herein. --

Amendments to the Claims:

Claims 63-73 and 99-106 were cancelled via the Preliminary Amendment of September 26, 2002. On January 30, 2004, Applicants provisionally elected with traverse the invention of Group I, namely claims 1-62. Although the outstanding Office Action indicates that the Office has withdrawn claims 63-106, Applicants believe that, in view of the previous cancellation of claims 63-73 and 99-106, the Office meant to indicate that claims 74-98 have been withdrawn.

Prior to further substantive examination, please cancel pending claims 1-32, 34, 35, and 55 without prejudice to their subsequent reintroduction into this application or their introduction into a related application. Claim 107 has been added. Claims 33, 36, 37, 40-44, 47, 49, 51, 53, 58 and 59 have been amended. Upon entry of this paper, claims 33, 36-54, 56-62, and 107 will be pending and under consideration in this case.

The following listing of claims replaces all prior versions and lists of claims in the application:

Listing of Claims:

1-32. (Cancelled)

33. (Currently Amended) A method of identifying a ~~candidate~~ molecule that binds to a large ribosomal subunit, the method comprising the steps of:

(a) ~~providing a molecular model of a ribofunctional locus of a large subunit of a ribosome, wherein the molecular model is based on atoms derived from an electron density map having a resolution of at least about 4.5 Å; and~~ providing a molecular model comprising one or more target regions selected from the group consisting of at least a portion of (i) a peptidyl transferase site, (ii) an A-site, (iii) a P-site, (iv) an E-site, (v) an elongation factor binding domain, (vi) a polypeptide exit tunnel, and (vii) a signal recognition particle (SRP) binding domain, from the atomic co-ordinates for *Haloarcula marismortui* large ribosomal subunit found on

Disk 1 under file name 1JJ2.RTF, 1JJ2.TXT, 1JJ2.PDB, PDB1FFK.DOC, or PDB1FFK.ENT, or deposited at the Protein Data Bank under accession number PDB ID: 1JJ2 or 1FFK, or derived from said *Haloarcula marismortui* atomic co-ordinates by molecular modeling;

(b) using the molecular model to identify a candidate molecule ~~having a surface complementary to the ribofunctional locus.~~ that can bind to the one or more target regions in the molecular model; and

(c) producing the candidate molecule identified in step (b).

34-35. (Cancelled)

36. (Currently Amended) The method of claim 33 ~~or 35~~, comprising the additional step of determining whether the candidate molecule modulates ribosomal activity.

37. (Currently Amended) The method of claim 36, comprising the additional step of ~~identifying~~ repeating one or more of steps (a) through (c) to identify a modified molecule.

38. (Original) The method of claim 37, comprising the additional step of producing the modified molecule.

39. (Original) The method of claim 38, comprising the additional step of determining whether the modified molecule modulates ribosomal activity.

40. (Currently Amended) The method of claim 39, comprising the additional step of, after determining whether the modified molecule modulates ribosomal activity, producing the modified molecule.

41. (Currently Amended) The method of claim 33, wherein the candidate molecule is an antibiotic ~~or an antibiotic analogue~~.

42. (Currently Amended) The method of claim 37, wherein the modified molecule is an antibiotic ~~or an antibiotic analogue~~.

43. (Currently Amended) The method of claim 41, wherein the antibiotic ~~or antibiotic analogue~~ is a macrolide.

44. (Currently Amended) The method of claim 33, wherein ~~the ribofunctional locus~~ the one or more target regions comprises at least a portion of an active site.

45. (Original) The method of claim 44, wherein the active site comprises at least a portion of a peptidyl transferase site.

46. (Original) The method of claim 44, wherein the peptidyl transferase site is defined by a plurality of residues set forth in Table 5A or Table 5B.

47. (Currently Amended) The method of claim 33, wherein ~~the ribofunctional locus~~ the one or more target regions comprises at least a portion of an A-site.

48. (Original) The method of claim 47, wherein the A-site is defined by a plurality of residues set forth in Table 6A or Table 6B.

49. (Currently Amended) The method of claim 33 or 47, wherein ~~the ribofunctional locus~~ the one or more target regions comprises a least a portion of a P-site.

50. (Original) The method of claim 49, wherein the P-site is defined by a plurality of residues set forth in Table 7A or Table 7B.

51. (Currently Amended) The method of claim 33 or 47, wherein ~~the ribofunctional locus~~ the one or more target regions comprises at least a portion of a polypeptide exit tunnel.

52. (Original) The method of claim 51, wherein the exit tunnel is defined by a plurality of residues set forth in Table 8A, Table 8B, Table 9, or Table 10.

53. (Currently Amended) The method of claim 49, wherein ~~the ribofunctional locus~~ the one or more target regions comprises at least a portion of a polypeptide exit tunnel.

54. (Original) The method of claim 53, wherein the exit tunnel is defined by a plurality of residues set forth in Table 8A, Table 8B, Table 9, or Table 10.

55. (Cancelled)

56. (Original) The method of claim 33, wherein the molecular model is in an electronic form.

57. (Original) The method of claim 33, wherein the molecular model is generated from atomic co-ordinates produced by molecular modeling.

58. (Currently Amended) The method of claim 33 or 57, wherein the molecular model is generated from atomic co-ordinates produced by homology modeling using at least a portion of the atomic co-ordinates deposited at the Protein Data Bank under accession number PDB ID: 1FFK, 1FFZ, 1FG0, 1JJ2, ~~1K73, 1KC8, 1K8A, 1KD1, or 1K9M~~ or recorded on Disk No. 1 under file name PDB1FFK.DOC, PDB1FFK.ENT, PDB1FFZ.DOC, PDB1FFZ.ENT, PDB1FG0.DOC, PDB1FG0.ENT, 1JJ2.RTF, 1JJ2.TXT, or 1JJ2.PDB.

59. (Currently Amended) The method of claim 33 or 57, wherein the molecular model is generated from atomic co-ordinates produced by molecular replacement using at least a portion of the atomic co-ordinates deposited at the Protein Data Bank under accession number PDB ID: 1FFK, 1FFZ, 1FG0, 1JJ2, ~~1K73, 1KC8, 1K8A, 1KD1, or 1K9M~~ or recorded on Disk No. 1 under file name PDB1FFK.DOC, PDB1FFK.ENT, PDB1FFZ.DOC, PDB1FFZ.ENT, PDB1FG0.DOC, PDB1FG0.ENT, 1JJ2.RTF, 1JJ2.TXT, or 1JJ2.PDB.

60. (Original) The method of claim 33, wherein the molecular model comprises residues that are conserved among one or more prokaryotic organisms.

61. (Original) The method of claim 33, wherein the molecular model comprises a residue that is present in a prokaryotic ribosome but is absent from a eukaryotic ribosome or a eukaryotic mitochondrial ribosome.

62. (Original) The method of claim 61, wherein the eukaryotic ribosome is a mammalian ribosome.

63-73. (Cancelled)

74-98. (Withdrawn)

99-106. (Cancelled)

107. (New) A method of identifying a molecule that binds to a large ribosomal subunit, the method comprising the steps of:

(a) providing a molecular model comprising one or more target regions selected from the group consisting of a peptidyl transferase site, an A-site, a P-site, an E-site, an elongation factor binding domain, a polypeptide exit tunnel, and a signal recognition particle (SRP) binding domain, from the atomic co-ordinates (i) for *Haloarcula marismortui* large ribosomal subunit found on Disk 1 under file name 1JJ2.RTF, 1JJ2.TXT, 1JJ2.PDB, PDB1FFK.DOC, or PDB1FFK.DOC, or deposited at the Protein Data Bank under accession number PDB ID: 1JJ2 or 1FFK, or (ii) derived from the *Haloarcula marismortui* atomic co-ordinates by molecular modeling;

(b) using the molecular model to identify a candidate molecule that can bind to the one or more target regions in the molecular model; and

(c) producing the candidate molecule identified in step (b).

REMARKS

Claims 1-32, 34, 35, and 55 have been cancelled without prejudice. Claim 107 has been added. Claims 33, 36, 37, 40-44, 47, 49, 51, 53, 58 and 59 have been amended. Upon entry of this paper, claims 33, 36-54, 56-62 and 107 will be pending and under consideration.

Claim 33, step (a) has been amended to recite the step of "providing a molecular model comprising one or more target regions selected from the group consisting of at least a portion of (i) a peptidyl transferase site, (ii) an A-site, (iii) a P-site, (iv) an E-site, (v) an elongation factor binding domain, (vi) a polypeptide exit tunnel, and (vii) a signal recognition particle (SRP) binding domain from the atomic co-ordinates for *Haloarcula marismortui* large ribosomal subunit found on Disk 1 under file name 1JJ2.RTF, 1JJ2.TXT, 1JJ2.PDB, PDB1FFK.DOC, or PDB1FFK.ENT, or deposited at the Protein Data Bank under accession number PDB ID: 1JJ2 or 1FFK, or derived from said *Haloarcula marismortui* atomic co-ordinates by molecular modeling." Step (b) of claim 33 has been amended to recite the step of "using the molecular model to identify a candidate molecule that can bind to the one or more target regions in the molecular model." In addition, step (c) has been added. Support for the amendments may be found, for example, in claims 33, 34, 35, 45, 47, 49, and 51, and on page 15, lines 17-25, page 32, lines 4-16, page 35, lines 3-20, page 39, lines 5-14, and the table appearing on page 185 of the application as originally filed.

Claim 37 has been amended to recite "the additional step of repeating one or more of steps (a) through (c) to identify a modified molecule." Support for the amendment may be found, for example, on page 84, line 1 of the application as originally filed. Claim 40 has been amended to specify that the production step occurs after determining whether the modified molecule modulates ribosomal activity. Support for the amendment may be found, for example, in claim 40 and on page 160, lines 21-23 of the application as originally filed. Claims 44, 47, 49, 51, and 53 have been amended to recite "one or more target regions" to correct antecedents in view of the amendment to claim 33. Support for the amendments to claims 58 and 59 may be found, for example, in the table appearing on page 185 of the application as filed. Support for new claim 107 can be found, for example, in claims 33, 34, 35, 45, 47, 49, and 51, and on page 15, lines 17-

25, page 35, lines 3-20, page 39, lines 5-14, and the table appearing on page 185 of the application as originally filed. Applicants believe that the amendments introduce no new matter.

In view of the amendments and/or cancellations to the claims, Applicants request that the inventorship of the application be amended pursuant to 37 C.F.R. 1.48(b) to delete Joseph A. Ippolito from the inventive entity because his invention is no longer being claimed in this application. The inventive entity of the claimed subject matter includes Thomas A. Steitz, Peter B. Moore, Poul Nissen, Nenad Ban and Jeffrey Hansen. In addition, Applicants include a check to cover the processing fee as required by 37 C.F.R. 1.48 (b)(2).

Applicants respectfully request that the Examiner consider the Supplemental Information Disclosure Statement, PTO-1449 form and the art cited thereon submitted to the Office on March 4, 2003. For convenience, Applicants enclose a copy of the Supplemental Information Disclosure Statement and PTO-1449 form. Applicants request that the Examiner initial each entry and then sign and date the PTO-1449 form, and then return a copy of the completed PTO-1449 form to the undersigned for completion of Applicants files.

The outstanding objections and rejections are discussed in the order in which they appear in the Office Action.

Restriction/Election Requirement

According to pages 2-7 of the outstanding Office Action, the Office issued a restriction to one of the following inventions under 35 U.S.C. §121 including Group I (claims 51-62), Group II (claims 63-98), Group III (claims 99-103), Group IV (claims 104 and 105), and Groups V through XIV (claim 106 to the extent that it relates to a particular antibiotic binding site). Applicants hereby confirm the provisional election with traverse of the invention of Group I, namely claims 1-62 as originally filed. Applicants believe that a search of the subject matter of Group I would necessarily include a search of the subject matter of Group II. The Office Action indicates that the claimed subject matter of both Groups I and II is classified as belonging to class 702, subclass 19. Accordingly, Applicants believe that it would not be unduly burdensome to search and examine the subject matter of Groups I and II. Applicants respectfully request rejoinder of Groups I and II.

Title Not Descriptive

According to page 7 the outstanding Office Action, the title presently stands objected to for not being descriptive. Applicants believe that the amended title overcomes this objection and, therefore, respectfully request that this objection be reconsidered and withdrawn.

Obviousness Double-Patenting Rejection

According to pages 7 through 9 of the outstanding Office Action, claims 33-62 presently stand rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 76 and 79-105 of co-pending U.S. Patent Application Serial No. 09/922,251.

Although Applicants disagree with the Office's position that the terms "complementary" and "binding specificity" are unclear, Applicants respectfully request that this provisional rejection be held in abeyance until the pending claims, but for any outstanding double patenting rejection, are deemed to be in condition for allowance. Applicants at that time intend to file a terminal disclaimer if appropriate under the circumstances.

Applicants wish to bring the following cases to the Examiner's attention to determine whether other potential double patenting issues may apply: U.S. Serial No. 09/635,708 (issued as U.S. Patent No. 6,638,908); U.S. Serial No. 10/391,491; U.S. Serial No. 10/391,289; U.S. Serial No. 10/072,634; and U.S. Serial No. 10/211,931.

Rejection Under 35 U.S.C. §101

According to pages 11-12 of the outstanding Office Action, claims 32, 33, 34, 36, 37 and 41-62 presently stand rejected under 35 U.S.C. §101 for allegedly being directed to non-statutory subject matter. Claims 32, 34 and 55 have been cancelled thereby obviating this rejection. Applicants respectfully traverse this rejection of claims 33, 36, 37, 41-54, and 56-62, for the following reasons.

Without acquiescing to the merits of this rejection, Applicants have introduced the limitation of claim 35 into independent claim 33. Claim 35 was not rejected on these grounds. Applicants submit that the amendment to claim 33 overcomes this rejection. Claims 36, 37, 41-

54 and 56-62 depend from and, therefore, incorporate the limitations of amended claim 33. In view of the foregoing, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Rejection Under 35 U.S.C. §112, First Paragraph

According to pages 11-12 of the outstanding Office Action, claims 3, 7, 21, 22, 58 and 59 presently stand rejected under 35 U.S.C. §112, first paragraph for allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the claimed invention. Claims 3, 7, 21 and 22 have been cancelled thereby obviating this rejection. Applicants respectfully traverse this rejection of claims 58 and 59, for the following reasons.

Claims 58 and 59 have been amended to include references to the atomic co-ordinates recorded on Compact Disk No. 1 under file names PDB1FFK.DOC, PDB1FFK.ENT, PDB1FFZ.DOC, PDB1FFZ.ENT, PDB1FG0.DOC, PDB1FG0.ENT, 1JJ2.RTF, 1JJ2.TXT, and 1JJ2.PDB. Applicants submit that the specification (see, for example, pages 184-185) and the compact disk containing these atomic co-ordinates comply fully with 37 C.F.R. 1.52(e). Applicants submit that the data recorded on Compact Disk No. 1 is incorporated properly into the application as filed, and that references to the atomic co-ordinates recorded on Compact Disk No. 1 in claims 58 and 59 is proper.

Applicants respectfully disagree with the Office's position that because "atomic coordinate information [in the Protein Data Bank] is continuously updated it is not clear what information is intended." Applicants understand that each PDB identifier (PDB ID) is associated with a specific set of atomic co-ordinates and that changes to the atomic co-ordinates require a new PDB ID to be assigned to the new set of atomic co-ordinates. See, for example, page 6 of the attached document entitled "PDB Data Deposition and Data Processing Procedures," which under the heading "**How can I replace coordinates?**" states "if the [co-ordinate] file has been released, the new set would receive a new ID code and should be deposited in a new [deposition] session." Accordingly, Applicants understand that a particular PDB identifier is associated with a particular set of atomic co-ordinates once those co-ordinates have been released.

In view of the foregoing, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Rejection Under 35 U.S.C. §112, Second Paragraph

According to pages 13 and 14 of the outstanding Office Action, certain terms in the claims presently stand rejected under 35 U.S.C. §112, second paragraph for allegedly being vague and indefinite.

Claims 5-7 were rejected on the grounds of being confusing. Applicants submit that claims 5-7 have been cancelled thereby obviating this rejection.

Claim 33 and all the claims depending from claim 33 have been rejected on the grounds that the term "complementary to the ribofunctional locus" is vague and indefinite. Although Applicants disagree, Applicants have amended claim 33 and, therefore, the claims depending from claim 33 to remove this language.

Claim 37 presently stands rejected on the grounds that the term "modified molecule" is vague and indefinite. Applicants respectfully disagree and submit that the skilled artisan would appreciate that the modified molecule of claim 37 differs in some way, i.e., is modified, from the candidate molecule identified in step (b) of claims 33 and 36.

Claim 40 presently stands rejected on the grounds that the language "the additional step of producing the modified molecule" is not clear. Although the Applicants disagree, Applicants have amended claim 40 to recite that, "after determining whether the modified molecule modulates ribosomal activity" the method then includes the step of "producing the modified molecule." This scenario would occur, for example, after testing has been completed and the modified molecule then is produced in commercially significant quantities. This concept is described, for example, in the fifth paragraph appearing on page 160 of the application as filed.

Claims 41 and 42 presently stand rejected on the grounds that the term "antibiotic analogue" is vague and indefinite. Applicants believe that this term is unnecessary and, therefore, have removed this term from claims 41, 42 and (although not mentioned in the Office Action) claim 43.

In view of the foregoing amendments and remarks, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Rejection Under 35 U.S.C. §103

According to pages 14-16 of the outstanding Office Action, claims 1-31 presently stand rejected as being obvious in view of the teachings of Brunger *et al.* (2000) Acta Crystallographica, D54, Part 9, 905-921. Claims 1-31 have been cancelled thereby rendering this rejection moot. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Objection to the Disclosure

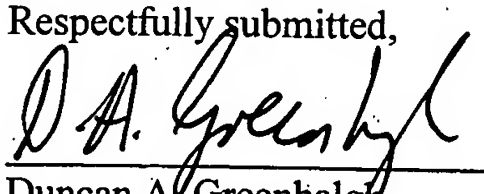
According to page 16 of the outstanding Office Action, the disclosure is objected to for inclusion of embedded hyperlinks and/or other forms of browser-executable code.

Applicants submit that the hyperlinks are not necessary for the application's compliance with 35 U.S.C. 112, first paragraph or that they be active. However, because the identified web sites may be of general interest to the skilled artisan reviewing the application, Applicants have attempted to deactivate the links via the amendments described herein. In view of the foregoing, Applicants request that this objection be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe that the case is in condition for immediate allowance. Early favorable action is respectfully solicited. The Examiner is invited to contact the undersigned with any questions about this paper.

Respectfully submitted,



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